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Original Article

Nasal polyposis in lung transplant recipients with cystic fibrosis

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Abstract

Background: Chronic rhinosinusitis with nasal polyposis is common in patients with cystic fibrosis (CF). There are still many open questions regarding factors related to this condition. Furthermore, the prevalence of nasal polyposis and its implications for the outcomes in lung transplant recipients with cystic fibrosis are unknown.
Methods: All CF patients who underwent lung transplantation at our centre between November 1992 and December 2009 were included. Nasal polyp status was determined endoscopically at time sinus surgery and its relationships to gender, age at lung transplantation, Liou raw score, body mass index, FEV_1%predicted, diabetes mellitus, pre-transplant pseudomonas colonisation of the sinuses and the lungs, pre-transplant corticosteroid use and type of mutation of the CFTR gene were analysed. The post-transplant survival times and the incidence of bronchiolitis obliterans syndrome in patients with or without nasal polyposis were compared.
Results: Nasal polyps were found in 19% (17 patients) of the 89 lung transplant recipients, whose data was available for statistical analysis. None of the factors analysed was related to the nasal polyp status. The post-transplant survival times and the incidence of bronchiolitis obliterans syndrome did not significantly differ between patients with or without nasal polyposis.
Conclusions: CF-related nasal polyposis occurs in a relevant fraction of lung transplant recipients. A specific effect of nasal polyposis on post-transplant outcome could not be confirmed. Nevertheless, there was a trend to NP recurrence in patients with post-transplant sinonasal pseudomonas colonisation and is a tendency of less chronic rejection in CF patients with nasal polyps.

Keywords: Cystic fibrosis; Lung transplantation; Chronic rhinosinusitis; Nasal polyposis; Survival; Bronchiolitis obliterans syndrome

1. Introduction

Chronic rhinosinusitis with nasal polyposis (NP) is common in patients with cystic fibrosis (CF), with an estimated prevalence of 6–48% [1–7]. Despite its frequency, there are still many open questions regarding the origin of polyp growth. Some argue that the CF genotype may play a major role [1,8–10], and chronic colonisation with *Pseudomonas aeruginosa* might be a co-factor for NP [11].

Some studies have suggested that CF patients with NP show milder lung disease and have better survival rates than patients without NP [1,5,6,9], whereas others found no relationship between NP status and the severity of CF [12]. Moreover, the influence of a potentially specific CF phenotype with NP on bronchiolitis obliterans syndrome (BOS) and survival after lung transplantation (LTx) is not known, but might have both practical and prognostic implications in this group of patients with terminal CF lung disease.

The aim of this study was to determine the prevalence of NP in CF patients undergoing lung transplantation, to identify potential predictors for NP and to examine the survival and cumulative incidence of BOS of lung transplant recipients with and without NP.

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2. Methods

All CF patients undergoing LTx at our centre between November 1992 and December 2009 were included in this study, and the data was collected retrospectively. The lung transplant recipients were followed until the end of December 2011, representing a minimum follow-up of two years per patient. The candidates for LTx were carefully selected following the international guidelines of the ISHLT Pulmonary Scientific Council [13]. The transplantation type was a sequential bilateral lung transplantation as described previously [14].

The standard protocol of immunosuppression (cyclosporine, azathioprine or mycophenolate mofetil and prednisolone) and induction therapy (anti-thymocyte globulin or basiliximab) was followed as described by Speich et al. [15]. On the basis of the sputum cultures, all patients were treated with a combination of at least two antibiotics for *Pseudomonas aeruginosa* (PA) for at least the first two weeks after LTx [14]. Further prophylactic therapy included cotrimoxazole, acyclovir/valacyclovir, oral itraconazole and nebulised amphotericin B. In addition, all transplant recipients with CF received a nebulised therapy with Colistin as prophylaxis against infection [14]. Inhalations with Colistin started immediately after LTx and were continued lifelong if patients had airway cultures positive for PA.

After the patient recovered from the transplantation, routine sinus surgery was performed as described previously [16]. Nasal polyp (NP) status was determined using the rigid endoscope at time of sinus surgery. The surgery consisted of an endoscopic fronto-spheno-ethmoidectomy as descried elsewhere [17,18]. In this procedure, all sinuses are widely opened and explored no matter how well they are pneumatised [16]. Daily nasal douching with isotonic saline solution was initiated on the second day after surgery. A potential relapse of NP was determined at the post-transplant follow-up visits by nasal endoscopy.

Microbiological sampling was performed with bronchoscopy and bronchoalveolar lavage (BAL) along with nasal endoscopy and aspiration of sinus secretions. Bacterial colonisation with PA was considered significant if bacterial counts were 10^4 colony-forming units/ml or more.

The diagnostic criteria for bronchiolitis obliterans syndrome (BOS) were applied as described elsewhere [19]: BOS 0 was defined as FEV_1 (forced expiratory volume in 1 s) >90% of baseline and FEF25-75 (mid-expiratory flow rate) >75% of baseline; BOS 0-p as FEV_1: 81 to 90% of baseline and/or FEF_{25-75}: ≤75% of baseline; BOS 1 as FEV_1: 66 to 80%; BOS 2 as FEV_1: 51 to 65%; and BOS 3, FEV_1: ≤50% of baseline. Estimated pre-LTx survival was calculated according to Liou et al. [20].

3. Statistical analysis

Descriptive statistics were used, and the mean and 95% confidence intervals (95% CI) are reported. Two groups were defined: Patients with nasal polyps (with NP) and without nasal polyps (without NP) at time of sinus surgery. Mann–Whitney tests and Fisher's Exact Tests (2×2 tables) were used to compare these groups, and a p-level <0.05 was considered as significant (two-tailed).

Survival and BOS following LTx were evaluated using Kaplan–Meier estimates. The groups with or without NP were compared with log rank tests. A multivariate analysis for the development of NP was performed. The following parameters were evaluated: gender, pre-transplant FEV_1, BMI, estimated survival without LTx, pre-transplant sinonasal and pulmonary PA colonisation (prePA-nose and prePA-lung), systemic pre-transplant corticosteroid treatment (preCS-use), pre-transplant diabetes (CFDM) and dF508 homozygosity. NP relapse rates and its relation to post-transplant sinonasal and pulmonary PA colonisation (postPA-nose and postPA-lung) were analysed using Fisher's Exact Tests (2×2 tables). IBM® SPSS® Statistics version 19 was used for the statistical analysis.

The institutional review board of the University Hospital Zurich (Kantonale Ethikkommission Zurich) approved this retrospective study.

4. Results

Five of the 94 CF patients did not undergo sinus surgery due to allograft deficiency, multiorgan failure or severe infection/sepsis and were excluded due to missing information on NP. The 89 evaluated patients (44 females, 49%) had a mean age of 26.9 years (95%CI 25.2–28.6 years) at LTx, a pre-LTx FEV_1 of 1.0 l (0.65–1.40 l) (26% of predicted FEV_1 (24–27%)) and an estimated 5-year survival without LTx of 33% (30–36%) (Table 1). Seventeen patients (19%) had nasal polyps by rigid endoscopy.

No difference was found regarding gender, pre-transplant FEV_1 or BMI, estimated survival without LTx, pre-transplant sinonasal or pulmonary PA colonisation, systemic pre-transplant corticosteroid treatment, pre-transplant diabetes or the presence or absence of dF508 homozygosity of the CFTR gene (Table 1). In the uni- and multivariate analysis none of the investigated parameters (gender, pre-transplant FEV_1, BMI, estimated survival without LTx, prePA-nose, prePA-lung, preCS-use, CFDM and type of mutation of the CFTR gene) favoured the development of NP.

Table 1
Characteristics of CF patients with and without nasal polyps (NP).

	With NP	Without NP
N, %	17 (19)	72 (81)
Female/male (*n*, %)	9/8 (53/47)	35/37 (49/51)
Age at LTx (year (95%CI))	26 (22–30)	27 (25–29)
Body mass index (kg/m^2, 95%CI)	16.6 (15.8–17.5)	17.7 (17.0–18.3)
FEV_1 (litres, 95%CI)	0.74 (0.65–0.83)	1.09 (0.62–1.55)
FEV_1%predicted (%,95%CI) (%,95%CI)	23 (19–26)	26 (25–28)
Survival without LTx at 5 years (%,95%CI)	31 (24–38)	33 (30–37)
PrePA-nose (*n*, %)	15 (88)	59 (82)
PrePA-lung (*n*, %)	15 (88)	55 (76)
PreCS-use (*n*, %)	4 (24)	23 (33)
dF508 homozygotes (*n*, %)	9 (53)	40 (56)
CFDM (*n*, %)	8 (47)	48 (67)

Recurrence of NP after sinus surgery was observed in 12 (71%) of the 17 patients who presented with NP at sinus surgery. Sinonasal colonisation with PA (postPA-nose) after LTx and sinus surgery was present in 10 (83%) of the 12 patients with a relapse of NP, which represents a trend towards NP recurrence in these patients ($p=0.083$). A statistical relationship between recurrence of NP and colonisation of the lung allograft (postPA-lung) could not be observed (Table 2).

Overall, the 1-, 5- and 10-year survival rates were 90.3±3%, 71±5% and 59±6%, respectively. One-, 5- and 10-year survival rates in patients with NP were 94±6, 77±10% and 61±13% compared with 89±4%, 69±6% and 59±7%, respectively, in patients without NP (Fig. 1). No significant difference was found regarding the development of BOS in the two groups (88±7% of the patients with NP were free from BOS1 compared with 78±5% in patients without NP). Nevertheless, there was a tendency towards a lower frequency of BOS stage 1 in the later post-transplant phase in patients with NP (Fig. 1).

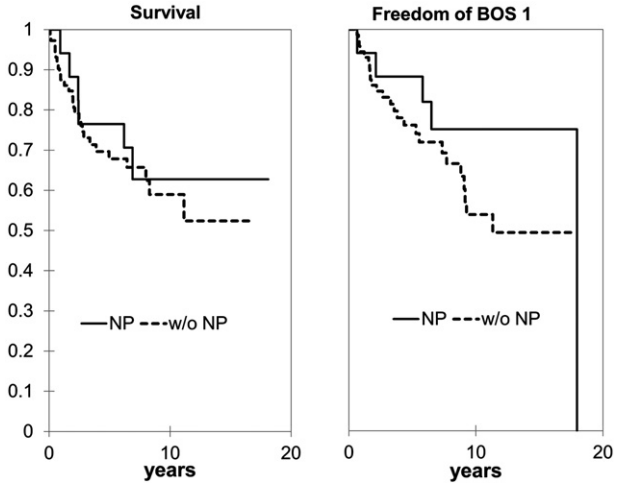

Fig. 1. Survival and freedom of BOS 1 in CF patients with nasal polyps (NP) and without (w/o NP).

5. Discussion

We report four major findings: 1.) NP was observed in almost one fifth of the lung transplant recipients with CF; 2.) we could not find predictors for the development of NP in end-stage CF patients; 3.) there is a trend towards NP recurrence in patients with sinonasal PA colonisation after LTx and sinus surgery and 4.) post-transplant survival of patients with NP did not differ significantly from survival of patients without NP and cumulative incidence of BOS showed a non-statistically significant association with NP status.

5.1. Prevalence of NP

The prevalence of NP in patients with end-stage CF lung disease requiring LTx does not seem to differ significantly from other CF patients [1–7]. Some authors have observed a milder lung disease in CF patients with NP [1,5,6,9]. If these findings were true, one would expect a lower prevalence of NP in lung transplant recipients with CF compared with other groups of CF patients. On the contrary, the prevalence of NP in our patients lies within the range of prevalence data reported in the literature [1–7]. However, a direct control group of CF patients, who did not require LTx, is not included in our study, given that our experimental design focused on lung transplant recipients. Therefore, direct comparisons of NP prevalence in patients with or without LTx will require additional research.

In our cohort, detection of NP was based on endoscopic examination. The value of radiologic imaging in the diagnosis of sinonasal disease of CF patients was discussed in the literature [21,22]. Whereas CT of the sinuses is able to localise sinonasal disease and show its extent, it cannot distinguish between thickened mucosa and infectious material. It was therefore proposed to use MR imaging to differentiate pus-filled areas from mucosal thickening without infection. Thereafter, the pus-filled areas could be selectively eradicated by surgery and patients might be spared from unnecessary radiation by CT. Furthermore, patients may be followed by MRI to not to miss recurrent infection [21,22].

As it was published in earlier studies [16,17], the goal of our surgical concept of post-transplant sinus surgery in lung transplant recipients with CF – together with a meticulous daily nasal care – is to reduce sinonasal colonisation and to prevent subsequent lung allograft infections with bacterial germs. For these purposes, all sinuses have to be widely opened no matter if they contain infectious fluid retentions or polyp tissue. To plan and perform this extensive surgical procedure, preoperative CT examination of the sinuses is crucial [23] and cannot be replaced by MRI due to its deficit in displaying the complex osseous structures of the viscerocranium. After having performed the extensive fronto-spheno-ethmoidectomy, the patient's sinuses may be examined easily with the rigid endoscope at the follow-up visits that is why there is no need for regular radiologic follow-up examinations as long there is no indication for revision surgery.

Table 2
Nasal polyp (NP) recurrence and colonisation with *Pseudomonas aeruginosa* (PA) after endoscopic sinus surgery.

		NP recurrence	
		Yes (*n*, %)	No (*n*, %)
PostPA-nose *	Yes (*n*, %)	10 (59)	2 (12)
	No (*n*, %)	2 (12)	3 (18)
PostPA-lung	Yes (*n*, %)	7 (41)	1 (6)
	No (*n*, %)	5 (29)	4 (24)

* Fisher's Exact Test $p=0.083$.

5.2. Predictors for nasal polyps and nasal polyp recurrence

None of the investigated factors (gender, age at LTx, Liou raw score, BMI, FEV_1%predicted, CFDM, prePA-nose, prePA-lung, preCS-use nor the presence or absence of dF508 homozygosity) was predictive for the development of nasal polyps in our population with end-stage lung disease.

Although some authors have found a correlation of NP growth with specific CFTR gene mutations, a relationship to dF508 homozygosity was not confirmed [1,8–10]. We rather suggest that NP is a feature of CF, which is sporadically associated with all degrees of CF severity [4,12].

Furthermore, pre-transplant PA infections were not related to the development of NP. Kingdom et al. [1] as well as Henriksson et al. [4] claimed that colonisation with PA is secondary to the chronic rhinosinusitis associated with NP. In contrast, Raj et al. [11] hypothesised that NP is secondary to an atopic inflammatory process against the colonised PA.

Regardless if the CF-related NP is secondary to a chronic colonisation with PA or if the appearance of PA is a result of the presence of NP, it is important to assess sinonasal colonisation with PA and other pathogens before and after LTx. It is known that chronic bacterial infection with PA leads to unopposed neutrophil elastase. This correlates with poor outcome due to bronchiolitis obliterans syndrome (BOS) and progressive irreversible graft dysfunction [24]. Walter et al. [25] and recently Mainz et al. [26] demonstrated that lung allografts became re-infected with the identical genotype of PA as it was harboured in the explanted lungs. It was hypothesised that the upper airways act as a reservoir from which bacterial germs spread to the lower airways. Our own data, published in 2004 [17] and 2012 [16], supports this hypothesis and underline the importance of post-transplant sinus surgery along with a meticulous daily nasal care, which reduces bacterial colonisation of the lung allograft significantly. Despite the absence of a statistical relationship of the NP status and the pre-transplant colonisation of the sinuses or the lung with PA, there is a trend towards recurrence of NP in patients who are colonised with PA after LTx. Regarding this trend, further studies have to investigate the recurrence of NP according to the colonisation with CF-relevant bacterial germs and its influence on post-transplant outcome.

In our view, several observations suggest that it is unlikely that an atopic inflammatory process induces NP in CF patients. First, atopic responses would be characterised by eosinophils in polyp tissue. In contrast, the inflammatory responses in NP of CF patients are predominantly neutrophilic [27]. Allergy is likely secondary and co-exists in CF in one fifth of the patients [28,29]. It is, however, not possible to determine the prevalence of co-existing eosinophilic NP in our CF patients by histological examination due to the fact that several of our patients received high-dose systemic corticosteroids before LTx. It is well known that corticosteroids reduce eosinophilic inflammation in the nasal mucosa and polyps [30,31]. It therefore can be assumed that the studied NP mainly is neutrophilic; a reduction of polyps would be expected by the high-dose systemic corticosteroids in the case of predominantly eosinophilic polyps.

In our population, we could not find a relationship of pre-transplant systemic use of corticosteroid and NP. A recent review of Mainz and Koitschev [27] on the pathogenesis and management of NP in CF attributed some effect in polyp shrinkage and symptom relief in cases of limited NP to topical nasal corticosteroids. However, only one double-blinded, placebo-controlled, randomized study exists on this topic [3] and the risk of bias in this work remains rather high. Patient's follow-up was considerably short (6 weeks) and more than half of the patients did not complete the course. Due to the lack of evidence in post-transplant NP and in fact that all post-transplant patients are under a high immunosuppressive regimen, our treatment concept of post-transplant CF-related NP does not include the use of topical nasal steroids.

5.3. Post-transplant survival and cumulative incidence of BOS

A potentially specific CF phenotype with increased survival after LTx might have practical and prognostic implications regarding the subgroup of CF patients with terminal lung disease awaiting LTx. Pre-transplant CF patients with NP might represent such a distinct subgroup with milder pulmonary disease and better survival [1,5,6,9]. However, we could not confirm that CF patients with NP had a better survival after lung transplantation and incidence of BOS did not differ significantly between patients with and without NP. However, there was a trend toward a lower prevalence of BOS stage 1 in the later post-transplant phase. This finding potentially could be explained by the Th2 polarisation with high IL5- and IgE-concentrations of CF patients with NP in contrast to CF patients without NP, who show a Th1 polarisation with high IFN-ϒ and TGF-β [32]. Th1 proinflammatory cytokines like IFN-ϒ, TGF-β and TNF-α are associated with the development of BOS after LTx [33], while the number of the IL5- and IL10-producing Th2 cells is significantly lower than in stable patients without BOS [34]. This trend merits further investigation.

6. Conclusions

CF-associated NP was not related to dF508 homozygosity or other predictors and occurred sporadically in our cohort of CF lung transplant recipients with a prevalence of 19%. We could not confirm any relationship of a specific CF phenotype (with NP) to post-transplant survival. Nevertheless, there was a trend to NP recurrence in patients with post-transplant sinonasal PA colonisation and a tendency of lesser BOS 1 in patients with the NP phenotype. These trends need to be investigated in further studies.

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